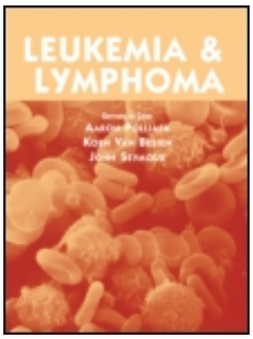

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COMMENTARY

Regulatory T cells in chronic lymphocytic leukemia: some progress and a bit of "tolerance" in understanding disease progression

Chava Perry[1] & Aaron Polliack[2]

[1]*Department of Hematology and Bone Marrow Transplantation, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel and* [2]*Department of Hematology, Hadassah University Hospital and Hebrew University Medical School, Jerusalem, Israel*

Tumors exploit a variety of mechanisms to actively suppress host immunity and generate an immune-subversive milieu [1]. CD4 + CD25^{high}FOXP3 + regulatory T cells (Tregs) are involved in the control of peripheral immunity, inducing immune tolerance by suppressing host immunity as well as anti-cancer immunity [1–3]. Increasing evidence supports the presence of elevated Treg counts in patients with solid tumors and some hemato-oncological malignancies, which helps to create a dysregulated immune-suppressive environment and provides an additional mechanism for reducing general immunity in these patients [2,4,5]. However, there are conflicting data reported regarding the presence of Tregs and their association with good prognosis in some lymphomas. In patients with follicular lymphoma, the presence of increased numbers of Tregs infiltrating the involved lymph nodes predicts for improved survival, although the suppressive function of Tregs was not examined [6]. In Hodgkin lymphoma a reduced number of Tregs appears to be associated with poor prognosis [7], while in patients with multiple myeloma both the number and function of Tregs have been shown to be reduced [8].

In this issue of ***Leukemia and Lymphoma***, Lad *et al*. evaluate the relationship between peripheral blood Tregs and the severity of chronic lymphocytic leukemia (CLL) at diagnosis, during disease progression and at the time of development of autoimmune cytopenia, in "therapy naive" patients [9]. Although the cohort is relatively small and consists of only 32 patients, it provides an interesting evaluation of the CLL population in India, where this type of leukemia is far less common than in Western countries. As described in other studies [4,10], Treg levels were elevated in patients with CLL compared to matched controls [9], and a progressive increase of this cell compartment was detected in advanced stages of the disease. While the differences in Treg percentages were not found to be statistically significant, there was a definite and significant increase in absolute Treg cell numbers in patients with advanced disease (Binet stage C) compared to those with earlier stages (Binet A and B).

As reported by others in earlier studies [4], Lad *et al*. [9] were unable to demonstrate an association between absolute Treg counts and other well established adverse prognostic factors for CLL, such as ZAP-70 positivity and increased CD38 expression. Nevertheless, they describe a strong inverse correlation between both the percentage and the absolute Treg cell numbers and lymphocyte doubling time (LDT). LTD has already been shown to predict time to first treatment in patients with early stage CLL [11]. Most recently, D'Arena *et al*. reported that the absolute number of Tregs could be used independently to predict time to treatment in patients with early stage CLL and to identify those cases with Rai stage 0 CLL who are at a higher risk of eventually requiring therapy [12]. In this study, baseline absolute Treg counts did not differ in patients who eventually had disease progression and those who did not progress, but this is most probably related in some way to the short follow-up period of this series of patients.

In the study reported here [9], Tregs were evaluated by flow cytometry using multi-color staining of CD4+, CD25^{high}, CD127^{low} and FOXP3+. In this regard, it is of interest to recall that Beyer *et al*. reported that a significant proportion of CD127^{low}FOXP3 + Treg cells expressed only low levels of CD25 [13], implying that the previously reported expansion of CD25 + Treg cells appears to underestimate the true pool of Treg cells present. This observation provides strong support for the superiority of the combined CD127 and FOXP3 analysis rather than the CD25 and FOXP3 assessment for further quantification of Treg cells. This may provide yet another explanation for the inability to detect differences in Treg cell levels in patients with early or intermediate stage CLL and to distinguish between those patients with progressive and non-progressive disease.

Lad *et al*. also reported that absolute Treg counts were significantly higher in patients with CLL developing

Correspondence: Dr. Chava Perry, MD, PhD, Department of Hematology and Bone Marrow Transplantation, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel-Aviv, Israel, 64239. Tel: 972(3)6973576. Fax: 972(3)6974452. E-mail: chavap@tlvmc.gov.il

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autoimmune cytopenias [9]. These results relating to autoimmune stigmata in CLL are somewhat surprising, taking into account that Tregs are actively involved in the induction of immune tolerance, and the fact that reduced functional activity of Tregs results in breakdown of tolerance and an increased susceptibility to autoimmune diseases [1]. In this respect it is noteworthy that in cutaneous T cell lymphoma, the suppressive function of Tregs has been shown to decrease during disease progression [14]. However, seeing that increased Treg cell numbers are associated with progressive disease, it is possible that the dynamic process of CLL progression may on its own interfere with the immune tolerance imposed by Tregs. In this regard, Ramsay *et al*. very recently reported that multiple inhibitory ligands co-opted by CLL B cells induce impaired immunologic synapse function in global T cell populations, thereby affecting the ability of T cells to form functional synapses with antigen presenting cells (APCs) [15]. Although this finding was reported as yet another mechanism utilized by tumor cells to evade the immune system, one could hypothesize that it is possible that this mechanism also affects Treg function. This may at least partially explain the correlation between increased Treg levels and the development of autoimmune cytopenias as reported by Lad *et al*. [9].

This study of the relatively rare population of Indian patients with CLL supports the concept that documentation of baseline absolute Treg cell counts using this relatively easy methodology may be useful to implement and apply as an independent prognostic factor for patients with CLL, and could help to evaluate disease severity and predict eventual progression in this disease.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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